
The International Society for Traumatic Stress Studies New Guidelines for the Prevention and Treatment of Posttraumatic Stress Disorder: Methodology and Development Process

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Over the last two decades, treatment guidelines have become major aids in the delivery of evidence-based care and improvement of clinical outcomes. The International Society for Traumatic Stress Studies (ISTSS) produced the first guidelines for the prevention and treatment of posttraumatic stress disorder (PTSD) in 2000 and published its latest recommendations, along with position papers on complex PTSD (CPTSD), in November 2018. A rigorous methodology was developed and followed; scoping questions were posed, systematic reviews were undertaken, and 361 randomized controlled trials were included according to the a priori agreed inclusion criteria. In total, 208 meta-analyses were conducted and used to generate 125 recommendations (101 for adults and 24 for children and adolescents) for specific prevention and treatment interventions, using an agreed definition of clinical importance and recommendation setting algorithm. There were eight *strong*, eight *standard*, five *low effect*, 26 *emerging evidence*, and 78 *insufficient evidence to recommend* recommendations. The inclusion of separate scoping questions on treatments for complex presentations of PTSD was considered but decided against due to definitional issues and the virtual absence of studies specifically designed to clearly answer possible scoping questions in this area. Narrative reviews were undertaken and position papers prepared (one for adults and one for children and adolescents) to consider the current issues around CPTSD and make recommendations to facilitate further research. This paper describes the methodology and results of the ISTSS Guideline process and considers the interpretation and implementation of the recommendations.

The authors would like to recognize the major contribution Dr. Lutz Goldbeck made to this work before he tragically died on October 30, 2017. The authors would like to acknowledge the support they received from Cardiff University's Traumatic Stress Research Group, The Cochrane Collaboration and The United Kingdom's National Institute for Health and Care Excellence in undertaking the systematic reviews and meta-analyses required for the Guidelines. The authors would also like to acknowledge the International Society for Traumatic Stress Studies (ISTSS) for providing some funding to support meetings and contributions from non-ISTSS members to the development of the Guidelines.

Jonathan Bisson, Catrin Lewis, Neil Roberts, and Candice Monson have developed Internet-based guided self-help programs to treat posttraumatic stress disorder (PTSD) and may benefit from these financially. Marylene Cloitre developed an intervention of skills plus exposure therapy for the treatment of complex presentations of PTSD and has published a workbook about treatment of the effects of childhood trauma for which she receives royalties. Francine Shapiro developed Eye Movement Desensitization and Reprocessing (EMDR) as a treatment for PTSD and is the Executive Director of the EMDR Institute.

Keeping on top of the proliferation of evidence regarding the prevention and management of health conditions has become a major challenge. As a result, health care professionals, policy makers, and service planners, along with individuals seeking or using services, increasingly rely on syntheses of available evidence to inform what should be provided and sought. Guidelines, developed through syntheses of evidence, are now widely advocated and followed. The International Society of Traumatic Stress Studies (ISTSS) produced the first guidelines for the prevention and treatment of posttraumatic stress disorder (PTSD) in 2000 (Foa, Keane, & Friedman, 2000), which were updated in 2009 (Foa, Keane, Friedman, & Cohen, 2009). The goal of this paper is to describe the development and facilitate the interpretation of the third version of the ISTSS Guidelines for the Prevention and Treatment of PTSD (ISTSS, 2018).

Determining how to interpret and implement guidelines in real-life settings can be difficult (Shekelle, 2018) and is made more complicated when different guidelines for the same condition draw different conclusions. The prevention and treatment of PTSD is a good example of this, with a number of guidelines from reputable sources, including the United Kingdom's National Institute for Health and Care Excellence (NICE; 2005), American Psychological Association (APA; 2017), U.S. Veterans Affairs and Department of Defense (VA/DoD; 2017), Phoenix Australia—Centre for Posttraumatic Mental Health (Phoenix Australia; 2013), and the ISTSS, providing overlapping but nonidentical recommendations in recent years (Forbes et al., 2010; Hamblen et al., 2018). The unavoidable conclusion is that guideline development is an imprecise science, with multiple degrees of freedom in the process, and the subsequent clinical recommendations may vary depending on the methodology used. This situation has resulted in calls for more standardization of guideline development and a more harmonious approach among guideline developers in the future (Institute of Medicine [IoM], 2011).

It is widely advocated that guideline developers rely on systematic reviews of research evidence, with quality and strength of evidence being taken into account before determining how strongly to recommend a particular intervention (Grading of Recommendations Assessment, Development and Evaluation [GRADE], 2018; IoM, 2011). This has, inevitably, led to the adoption of a hierarchy of evidence. Most such hierarchies consider randomized controlled trials (RCTs) to be the gold standard in determining what does and does not work (Eccles & Mason, 2001). Critics argue, however, that potentially im-

portant evidence generated outside RCTs is ignored and can devalue the recommendations made (Henriques, 2018). This concern echoes the sentiments of the founders of evidence-based practice who said, "Good healthcare professionals use both individual clinical expertise and the best available external evidence, and neither alone is enough." (Sackett et al., 1996).

Taking a more inclusive approach to sources of evidence offers the opportunity to include treatment approaches that have not been subjected to RCTs. However, this approach also comes with costs. The interpretation and comparison of results from different research designs is complicated and carries the risk of interventions that lack robust evidence being recommended more strongly than they should be. The inferences that can be drawn from study designs other than a well-controlled RCT may be very biased and, therefore, not yield sufficient information to make evidence-based recommendations. The first two versions of the ISTSS Guidelines took a more inclusive approach to the evidence, and recommendations were based on methodologically variable reviews of the literature by individuals with an interest in a particular topic area. Although this reflected common practice at the time, this approach is inconsistent with current standards and can be criticized for not adopting a priori decision rules that are objectively applied. More recent PTSD guidelines have adopted a more standardized methodology (e.g. APA, 2017; NICE, 2018a; Phoenix Australia, 2013; VA/DoD, 2017; World Health Organization [WHO], 2013) whereby specific questions are developed and independent systematic reviews undertaken to answer them, with experts following more formal processes to determine final recommendations.

With this backdrop, in 2015, the ISTSS Board of Directors decided to update its prevention and treatment guidelines for PTSD. It sought to generate guidelines through a robust methodological process that would be helpful to the field of traumatic stress. The resulting guidelines provide practitioners, service planners, policy makers, people with lived experience of PTSD, and other relevant stakeholders with accurate information on what works and what does not work to prevent or treat PTSD. This effort resulted in the publication of the ISTSS Guidelines for the Prevention and Treatment of PTSD recommendations and position papers in November 2018 (ISTSS, 2018). These publications will be complemented by the final part of the updated ISTSS Guidelines, the third edition of the *Effective Treatments for PTSD* book, due to be published at the end of 2019, with a primary goal of providing a resource for clinicians to apply the recommendations to clinical practice.

Dr. Shapiro has published books about EMDR therapy and the treatment of trauma and received royalties for these.

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DOI: 10.1002/jts.22421

Method

The ISTSS Board appointed an ISTSS Guidelines Committee (i.e., the authors of this paper) to develop its guidelines. The committee adopted a methodology that involved three distinct steps: (a) development of scoping questions to guide the review, (b) systematic reviews of the literature to identify

RCTs that could answer the a priori scoping questions, and (c) meta-analyses of usable data from the included studies to allow the generation of recommendations for prevention and treatment interventions.

Scoping Questions

The committee agreed on draft scoping questions in a Population, Intervention, Comparator, and Outcomes (PICO; Schardt, Adams, Owens, Keitz, & Fontelo, 2007) format for the prevention and treatment of PTSD in children, adolescents, and adults (e.g., “For adults with PTSD, do psychological treatments, when compared to treatment as usual, waitlist, or no treatment, result in a clinically important reduction of symptoms, improved functioning/quality of life, presence of disorder, or adverse effects?”). Separate draft scoping questions were developed to address the prevention or treatment of PTSD (clinically relevant posttraumatic stress symptoms in the case of children and adolescents). The committee consulted on the draft scoping questions with the ISTSS membership and reference groups of practitioners and nonpractitioner consumers for feedback before presentation to and approval by the ISTSS Board.

Inclusion of separate scoping questions on treatments for complex presentations of PTSD for both adults and children and adolescents was considered but decided against due to issues defining complex PTSD (CPTSD) and the virtual absence of studies specifically designed to clearly answer possible scoping questions in this area. The committee decided, therefore, to undertake a narrative review and prepare position papers (one for adults and one for children and adolescents) to consider the current issues around CPTSD and make recommendations to facilitate further research.

Systematic Reviews and Meta-Analyses

The committee identified high-quality systematic reviews developed by the Cochrane Collaboration, NICE, and WHO that addressed all the scoping questions except those pertaining to nonpsychological and nonpharmacological interventions. The RCTs included in these reviews were used as the basis of the evidence to be considered for the ISTSS guidelines. Existing reviews (Bisson, Andrew, Roberts, Cooper, & Lewis, 2013; Hoskins et al., 2015; Lewis, Roberts, Bethell, & Bisson, 2015; NICE, 2018b; Roberts, Kitchiner, Kenardy, & Bisson, 2009, 2010; Rose, Bisson, Churchill, Wessely, 2005; Sijbrandij, Kleiboer, Bisson, Barbui, & Cuijpers, 2015) were supplemented with additional systematic searches for more recent RCTs and by asking experts in the field as well as the ISTSS membership to identify any studies that might have been omitted. New systematic reviews were undertaken for the nonpsychological and nonpharmacological scoping questions. The Cochrane Collaboration Mental Health Disorders Group completed additional searches, using their comprehensive search strategies to identify RCTs of any intervention designed to prevent or treat PTSD

that were published during the period of January 1, 2008, to March 31, 2018.

Studies included in existing systematic reviews and newly identified studies were assessed against the agreed-upon inclusion criteria for the ISTSS Guidelines prior to undertaking the additional searches (see Table 1). Two researchers independently extracted data from included studies. When data were not available in the published article, the study authors were contacted and asked to provide them. Two researchers, using the Cochrane Collaboration’s risk of bias rating tool (Higgins & Green, 2011), rated the quality of all included studies for which data were available. The Cochrane Collaboration’s risk of bias criteria determine low-, uncertain, or high-risk ratings for random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias.

All available data addressing specific scoping questions were meta-analyzed using Revman (Version 5.3) software (The Nordic Cochrane Centre, 2014). The evidence for each of the scoping questions was summarized and its quality assessed using the GRADE system with its four levels of evidence: (a) high quality (further research is very unlikely to change our confidence in the estimate of effect), (b) moderate quality (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate), (c) low quality (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate), and (d) very low quality (we are very uncertain about the estimate). The evidence summaries and quality assessments were then used to generate draft recommendations using the algorithm described below. The draft recommendations were posted on the ISTSS website during August and September 2018 for a period of consultation by ISTSS members. Feedback from ISTSS members was reviewed and incorporated into the final recommendations, which were presented to and approved by the ISTSS Board in October 2018 and presented publicly at the annual ISTSS meeting in November 2018.

Definition of Clinical Importance and Recommendation Setting

In order to generate recommendations from the results of the meta-analyses, the committee developed a definition of clinical importance (shown in Table 2) following consultation with ISTSS members and the ISTSS Board. An algorithm was developed to allow for the systematic and objective agreement of recommendations after scrutiny of the meta-analyses pertaining to individual scoping questions. Consideration was given to magnitude of change, strength and quality of evidence, and any other important factors (e.g., adverse effects). Five different levels of recommendation were possible, as shown in Table 3. It was agreed that having five different levels

Table 1
Inclusion Criteria for Included Studies

| Studies | Inclusion Criteria |
|---------------------------------|---|
| All Studies | <ul style="list-style-type: none"> • Any RCT (including cluster and cross-over trials) evaluating the efficacy of interventions aimed at preventing (within 3 months of the traumatic event), treating, or reducing symptoms of PTSD. • Study participants have been exposed to a traumatic event as specified by PTSD diagnostic criteria for <i>DSM-III</i>, <i>DSM-III-R</i>, <i>DSM-IV</i>, <i>DSM-5</i>, <i>ICD-9</i>, <i>ICD-10</i>, or <i>ICD-11</i>. • Eligible comparator interventions for psychosocial interventions: waitlist, treatment as usual, symptom monitoring, repeated assessment, other minimal attention control group, or an alternative psychological treatment. • Eligible comparator interventions for pharmacological interventions: placebo, other pharmacological or psychosocial intervention. • The RCT is not solely a dismantling study. • Study outcomes include a standardized measure of PTSD symptoms (either clinician-administered or self-report). • No restriction on the basis of severity of PTSD symptoms or the type of traumatic event. • Individual, group, and couple interventions. • No minimum sample size. • Only studies published in English. • Unpublished studies eligible. |
| Early Intervention studies only | <ul style="list-style-type: none"> • Intervention begins no later than 3 months after the traumatic event. • Intervention is not provided pretrauma. |
| Treatment studies only | <ul style="list-style-type: none"> • For adults, at least 70% of participants required to be diagnosed with PTSD according to <i>DSM</i> or <i>ICD</i> criteria by means of a structured interview or diagnosis by a clinician. • For children and adolescents, at least 70% diagnosed with partial or full <i>DSM</i> or <i>ICD</i> PTSD by means of a structured interview or diagnosis by a clinician (partial PTSD is defined as at least one symptom per cluster and presence of impairment), or score above a standard cutoff of a validated self-report measure. • Duration of PTSD symptoms required to be 3 months or more. • No restrictions on the basis of comorbidity, but PTSD required to be the primary diagnosis. |

Note. RCT = randomized controlled trial; PTSD = posttraumatic stress disorder; *DSM* = *Diagnostic and Statistical Manual of Mental Disorders*; *ICD* = *International Classification of Diseases*.

of recommendation would facilitate decision-making with respect to clinical care as well as future research. For example, the “emerging evidence” recommendation was included to identify interventions (including novel interventions) that require further evaluation and may hold promise for the future.

Results

Recommendation Overview

The searches identified 5,500 potential new studies, and scrutiny of these studies and those included in existing reviews resulted in 361 RCTs that fulfilled the criteria for inclusion in the meta-analyses. Of these studies, 327 (90.6%) provided data that were included in the meta-analyses and were used to generate evidence summaries. A total of 208 meta-analyses were completed and used to generate 125 individual recommendations (101 for adults and 24 for children and adolescents). There were eight strong, eight standard, five low effect, 26 emerging evidence, and 78 insufficient evidence to recommend recommendations. There was only one recommendation against

providing a specific intervention (“Individual psychological debriefing within the first 3 months of a traumatic event has emerging evidence of increasing the risk of clinically relevant posttraumatic stress symptoms in children and adolescents”). Table 4 provides an example of the recommendations made.

Complex PTSD Position Papers

The position papers on CPTSD for adults and children/adolescents note previous challenges, including the lack of clarity in the characterization of complex presentations of PTSD and, consequently, the lack of persuasive evidence regarding the phenomenon of CPTSD, its assessment, and its treatment (e.g., Karatzias et al., 2017; Shevlin et al., 2018). The papers introduce the *International Classification of Diseases* (11th rev.; *ICD-11*) diagnosis of CPTSD, emphasizing that the diagnosis is made on the basis of the symptom profile and not the type of trauma (Cloitre, Gavert, Brewin, Bryant, & Maercker, 2013). In children and adolescents, the importance of developmental considerations when assessing symptoms of CPTSD is emphasized.

Table 2
Definition of Clinical Importance

- PTSD symptom change was the primary outcome measure, and other outcomes (e.g., diagnosis, functioning, other symptom change, tolerability) were considered as secondary outcome measures.
- The clinically important definition was based on both magnitude of change and strength/quality of evidence.
- An intervention delivered 3 or more months after the traumatic event had to demonstrate an effect size, calculated as the standardized mean difference for continuous outcomes of >0.8 (<0.65 relative risk for binary outcomes) for waitlist control comparisons, >0.5 for attention control comparisons (no meaningful treatment, but same dosage of time/same number of sessions with a therapist), >0.4 for placebo control comparisons, and >0.2 for active treatment control comparisons.
- To be rated clinically important, an early intervention had to demonstrate an effect size for continuous outcomes of >0.5 for waitlist control comparisons (<0.8 relative risk for binary outcomes).
- If there was only one RCT, an intervention was not normally recommended as clinically important. Noninferiority RCT evidence alone was not enough to recommend an intervention as clinically important.
- Unless there was a GRADE quality of evidence rating of high or moderate, consideration was given to downgrading the strength of recommendation made with respect to clinical importance.
- The primary analysis for a particular question included data from all included studies. When available, this was clinician rated; when unavailable, self-report was included. In addition, analyses that included only clinician-rated data were also considered. The combination of these two analyses was considered along with the GRADE ratings and risk of bias ratings to determine the strength of recommendation.
- The 95% confidence interval range had to completely exclude the thresholds for the strongest level of recommendation (i.e., lower confidence interval of >0.8 for waitlist control comparisons of treatments).

Note. PTSD = posttraumatic stress disorder; RCT = randomized controlled trial; GRADE = Grading of Recommendations, Assessment, Development and Evaluation.

It is noted that some existing treatments have been shown to reduce the symptoms of CPTSD, with some evidence that assessment scores remain higher for individuals likely to have CPTSD than for those with a diagnosis of *ICD-11* PTSD (e.g., Sachser, Keller, & Goldbeck, 2016). The papers call for further research to determine optimal treatments for CPTSD. Possible approaches include increased dosing and/or adaptation of existing treatments, sequencing of treatment components, booster sessions, the addition of other (as yet unspecified)

Table 3
Levels of Recommendation

| Level | Definition |
|------------------------------------|---|
| Strong | Interventions with at least reasonable quality of evidence and the highest certainty of effect. |
| Standard | At least reasonable quality of evidence and lower certainty of effect. |
| Intervention with low effect | At least reasonable quality of evidence and high certainty of a low level of effect. |
| Emerging evidence | Lower quality of evidence and/or certainty of effect. |
| Insufficient evidence to recommend | Absence of evidence of effectiveness or ineffectiveness. |

components, and more flexible implementation of problem-specific treatment modules using a personalized approach. Innovations in research design and treatment formulation provide the opportunity to continue to improve outcomes for adults and children/adolescents with CPTSD. The CPTSD position papers have now replaced the ISTSS's previously published expert consensus treatment guidelines for CPTSD (Cloitre et al., 2012).

Discussion

The ISTSS Guidelines for the Prevention and Treatment of PTSD provide 125 recommendations generated through syntheses of current RCT evidence. These recommendations address 20 carefully selected scoping questions. The method and process adopted for this effort adhere to internationally recommended standards (IOM, 2011) and compare favorably with those used to develop other recent and commonly followed guidelines for the prevention and treatment of PTSD (APA, 2017; NICE, 2018b; Phoenix Australia, 2013; VA/DoD, 2018). Notably, as a result of strict adherence to the internationally recommended standards, this version of the guidelines reflects a substantial change in methodology compared to the two earlier guidelines produced by ISTSS. It is hoped that the new ISTSS Guidelines will be widely adopted across the world, shape clinical service provision for individuals exposed to traumatic events, inform the research agenda, and foster development of the field.

The review revealed a significant growth of RCT evidence in recent years. This has resulted in a strengthening of recommendations relative to earlier guidelines for certain interventions, such as cognitive behavioral therapy with a trauma focus (CBT-T) for children, CBT-T for caregivers and children, and Eye Movement Desensitization and Reprocessing (EMDR) for the treatment of PTSD in children and adolescents. The additional RCTs also provided the ability to consider different forms

Table 4
Recommendations for Psychological Treatment of Posttraumatic Stress Disorder (PTSD) in Adults

| Recommendation Level | Recommendations |
|------------------------------------|--|
| Strong recommendation | Cognitive processing therapy, cognitive therapy, EMDR, individual CBT with a trauma focus (undifferentiated), and prolonged exposure are recommended for the treatment of adults with PTSD. |
| Standard recommendation | CBT without a trauma focus, group CBT with a trauma focus, guided Internet-based CBT with a trauma focus, narrative exposure therapy, and present-centered therapy are recommended for the treatment of adults with PTSD. |
| Emerging evidence | Couples CBT with a trauma focus, group and individual CBT with a trauma focus, reconsolidation of traumatic memories, single-session CBT, written exposure therapy, and virtual reality therapy have emerging evidence of efficacy for the treatment of adults with PTSD. |
| Insufficient evidence to recommend | There is insufficient evidence to recommend brief eclectic psychotherapy for PTSD, dialogical exposure therapy, emotional freedom techniques, group interpersonal therapy, group stabilizing treatment, group supportive counseling, interpersonal psychotherapy, observed and experimental integration, psychodynamic psychotherapy, psychoeducation, relaxation training, REM desensitization, or supportive counseling for the treatment of adults with PTSD. |

Note. Summary of relevant scoping questions: For adults with PTSD, do psychological treatments when compared to treatment as usual, waitlist, no treatment, or other psychological treatments result in a clinically important reduction of symptoms, improved functioning/quality of life, presence of disorder, or adverse effects? EMDR = eye movement desensitization and reprocessing; CBT = cognitive behavioral therapy; REM = rapid eye movement.

of CBT-T separately and, consequently, to recommend some forms (e.g., cognitive processing therapy [CPT], cognitive therapy for PTSD, and prolonged exposure [PE]) more strongly than others (e.g., group CBT-T, narrative exposure therapy, and brief eclectic psychotherapy for PTSD). The emergence of interventions that may not be as effective as the strongest interventions for PTSD but, nevertheless, have the potential to make a real

difference to people with PTSD (e.g., facilitated Internet-based CBT-T, present-centered therapy, and some medications) and allow choice in treatment modalities is a major step forward.

The inclusion of an “emerging evidence” recommendation category allowed recognition of a number of novel and innovative prevention and treatment approaches (e.g., neurofeedback and yoga) that are absent from previous guidelines. It is important to remember that emerging evidence recommendations were usually based on one or two RCTs with very low GRADE ratings. It is likely that some will develop into effective and strongly recommended interventions with robust evidence of effect and that others will not fulfill their initial promise once further research is undertaken. As such, these can be considered as potential priority candidate interventions for further research and should not be considered as frontline approaches for the prevention and treatment of PTSD. Still, the committee saw value in highlighting this group of interventions above those with insufficient evidence to make any recommendation, notwithstanding the important adage that absence of evidence is not absence of effect.

Key strengths of the ISTSS Guidelines are the transparency and replicability of the process used. The committee established a priori agreement of key elements of the review and recommendation processes: scoping questions, inclusion and exclusion criteria for papers, definition of clinical importance, and a recommendation generation algorithm. Using a rigorous methodology across the varied scoping questions reduced the risk of inconsistency and conscious or unconscious bias of committee members impacting the recommendations made. In common with all prevention and treatment guidelines, there are also a number of limitations, and it is important that these are taken into account when interpreting and before implementing the recommendations.

The selection of the guidelines committee is a potential source of bias (IOM, 2011). All members of the ISTSS Guidelines Committee declared conflicts of interest, primarily as a result of allegiance to different psychological interventions. These were transparently declared but may have influenced outcomes. It has been argued that including members with conflicts of interest should be avoided or minimized (IOM, 2011; Shekelle, 2018). Having a committee with no conflict of interest risks having a committee without sufficient knowledge and expertise. The ISTSS Board was keen to include individuals with expertise (and, consequently, potential conflicts of interest) in various approaches to the prevention and treatment of PTSD in adults, children, and adolescents, as well as expertise in guideline development, systematic reviews, and meta-analysis.

The inclusion of only RCTs can be seen as a strength but also a limitation as it risks relying too heavily on, at times, low-quality RCTs while ignoring other possible sources of evidence (Bothwell, Greene, Podolsky, & Jones, 2016; Sackett, Rosenberg, Muir Gray, Haynes, & Richardson, 1996). Incorporating evidence from other sources, such as large observational cohort studies and nonrandomized controlled studies (e.g., effectiveness studies and “evidence from practice”), could

potentially contribute to a more accurate overall assessment of the effectiveness of a particular intervention and would allow consideration of effect from different perspectives. Unfortunately, this approach could also risk diluting higher-quality sources of evidence with weaker ones and drawing inferences without sufficient information to do so. Guideline developers are increasingly acknowledging this dilemma and recognize that RCT evidence is not the only source of helpful knowledge (NICE, 2018b). Irrespective of the sources of evidence used, recognition of the importance of other, real-world factors that may influence the adoption and implementation of recommendations is very important to the understanding of the real-world success of these treatments. The practice implications of the ISTSS Guidelines' recommendations will be the primary focus of the third edition of the *Effective Treatments for PTSD* book.

Another limitation is that only 20 scoping questions were addressed by the present reviews. This number reflected the committee's effort to balance the breadth of pertinent topics, the time and resources available to conduct the reviews, and the availability of published RCTs to address the questions. There are many other important questions concerning the prevention and treatment of PTSD that were not answered by the ISTSS Guidelines. These include preventative interventions for high-risk occupations, such as military and first-responders, delivered prior to exposure; comorbidity with other conditions, especially when PTSD is not the primary diagnosis; prevention beyond 3 months after traumatic events (e.g., there has been a lot of work from schools in traumatized populations trying to prevent the development of PTSD months and years after traumatic events occurred); the long-term effects of interventions; relative efficacy of pharmacological and psychological treatments; sequencing of treatment; augmentation treatment; and drug-assisted psychological treatment.

Another issue the committee encountered was that several high-quality RCTs were designed in a way that did not allow them to be included in the meta-analyses. For example, in the case of CPT, several methodologically strong studies did not compare CPT against usual treatment or waitlist control but instead compared different modes of delivery of CPT against each other (Morland et al., 2015) or used a novel RCT methodology that precluded inclusion in our meta-analyses (Galovski, Blain, Mott, Elwood, & Houle, 2012). Additionally, the significant number of CPT effectiveness studies demonstrating its applicability to a broad and diverse range of clinical populations and settings, while providing potentially very important information for clinicians, service planners, and policy makers, were not included due to failure to meet the RCT specifications. This may account for CPT having less evidence of efficacy against waitlist or usual care than other established treatments of PTSD that received a strong recommendation (e.g., EMDR and PE). Our algorithm did, however, allow a strong recommendation to be made for CPT on the basis of equivalence in head-to-head RCTs versus another strongly recommended treatment. The experience of the committee with CPT supports the need

for more innovative methodological approaches to the development of guidelines to include other sources of high-quality evidence.

Even among the RCTs included in the analyses, differences in the methodology employed varied between studies and may have impacted meta-analytic results and their interpretation. Issues encountered included the use of different measures of PTSD symptomatology, different treatment populations, different approaches to calculating means, and different ways of dealing with missing data. The committee made an a priori decision to use data in meta-analyses from as many eligible studies as possible. This meant including self-report data in the absence of clinician-reported data and completer-only data in the absence of intention-to-treat data. The inclusion of completer-only data may have contributed to bias, and it is important to note this when interpreting the results. Metaphorically, we compared apples of different varieties in individual meta-analyses but did not compare apples with pears.

Before the meta-analyses were performed, the committee considered and defined what level of effect represented a clinically important difference and incorporated this into an a priori agreed algorithm to determine different levels of recommendation. This is a major strength of the ISTSS Guidelines that adheres to recommended standards (GRADE) but requires judgment calls that inevitably influence the recommendations made. For example, the decision to require an effect size for placebo-controlled trials that was 50% of that required for waitlist and usual-care trials (standardized mean difference [SMD] = 0.8 vs. 0.4) may or may not be optimal although the decision was informed by previous guideline development work and expert opinion. It is almost impossible to argue against having a reduced threshold for placebo-controlled trials, but the magnitude of that reduction is open to debate. Similarly, the effect size threshold for active treatment control comparisons was SMD = 0.2 as it was agreed that active-treatment controls were likely to be more effective than placebo. Another decision, in line with many other guidelines, was to group waitlist and usual-care control conditions. Careful scrutiny of usual-care conditions reveals a variety of approaches ranging from minimal care to more extensive intervention, with the potential to influence outcomes quite significantly and to possibly cause some interventions to appear less effective than they actually are.

One measure of the effectiveness of these a priori decisions is that only five recommendation decisions (all concerning treatment) required the achievement of consensus through ISTSS Guidelines Committee discussion; the algorithm generated the other 120 recommendations. This 24:1 ratio is a strength of the methodological approach; strict adherence to a priori rules is not only relatively unique in PTSD guideline development but also likely to have a reduced risk of bias due to specific views of committee members.

The five committee decisions that were more subjective (upgrading CPT in adults and EMDR and Trauma-Focused CBT [TF-CBT] for children and adolescents; downgrading neurofeedback and transcranial magnetic stimulation in adults) were

made as a result of the a priori rules triggering reconsideration of algorithm-generated recommendations when a degree of doubt was present. Allowing any reconsideration clearly introduces the risk of bias, but this has to be balanced against unintended consequences of an algorithm that, although developed a priori, have the potential to generate spurious results. A different committee may have made different decisions, but those made by the ISTSS Guidelines Committee were carefully deliberated before achieving consensus and, importantly, occurred through an explicit and transparent process.

The ISTSS recommendations are based on the agreed primary outcome of PTSD symptomatology posttreatment. This was usually the primary outcome for included studies, but it risks ignoring or underplaying other important outcomes. Depression, anxiety, substance use, overall functioning, quality of life, and longer-term follow-up with respect to PTSD were not considered yet could have altered the recommendations if they were, as they have in other guidelines. For example, NICE recommends against psychological debriefing for adults on the basis of evidence of harm at longer-term follow-up (National Collaborating Centre for Mental Health, 2005); the ISTSS Guidelines concluded that there is insufficient evidence to recommend either way.

Significant clinical and statistical heterogeneity within the meta-analyses undertaken complicates interpretation, not least with respect to reliability and generalizability of some of the findings (Melsen, Bootsma, Rovers, & Bonten, 2014). For example, the use of hydrocortisone as an early pharmacological treatment following traumatic events in adults was given an emerging evidence recommendation based on RCTs of hospitalized inpatients following major surgery. It is very debatable as to how generalizable this finding would be to other populations, and hydrocortisone could not be recommended for routine use following traumatic events with the evidence available at present. The key implication of the emerging evidence recommendation for hydrocortisone is that it is a strong candidate for further research to determine its potential to prevent PTSD.

The studies included in the meta-analyses covered heterogeneous settings and populations. The majority of included studies were conducted in higher-income settings, and caution is required when applying the results to low- and middle-income settings. It cannot be assumed that interventions are always transferable; reassuringly, however, research has found that a number of effective treatments for PTSD are effective in different settings across the world (Bass et al., 2013). Whatever the heterogeneity, it is likely that some adaptations to processes adopted in research studies, based on local service configuration, will be needed to implement recommendations in an acceptable, effective, and sustainable manner. These and other factors—for example, variation in therapist competence, differences between grouped interventions and the number of sessions or dosage delivered, and the possibility of interventions causing adverse effects and being less well tolerated by some individuals than others—means that care should be taken in in-

terpreting recommendations and determining their implications for clinical practice.

Whatever the level of recommendation, a specific intervention is unlikely to be appropriate for all people with PTSD. Interventions should only be delivered after a thorough assessment of an individual's needs and, where possible, a discussion between the individual (and caregivers) and therapist, with clear information about the evidence base, potential benefits, and risks to allow informed decision-making and the development of a codetermined intervention plan. These issues will be covered in detail in the *Effective Treatments for PTSD* book.

The ISTSS Guidelines represent a high-quality addition to the existing guideline recommendations available to clinicians. Like all guidelines, the ISTSS Guidelines should be used with appropriate caution; they represent a tool to aid the prevention and treatment of PTSD rather than a document that mandates specific approaches. The ISTSS Guidelines should stimulate research to improve the effectiveness of interventions in the future and stimulate work to improve the methodology of guideline development. It is hoped that they will support the dissemination and implementation of evidence-based practices to reduce the impact of traumatic stress globally. Further work to develop appropriate public-facing materials, including decision aids, to facilitate this is under way.

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